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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,901	06/18/2001	Carol H. Miao	UOFW117396	1704

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/884,901	MIAO ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 15, 16, 24, 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *15, 36, and 37* is/are allowed.

6)☒ Claim(s) *1-4,16, 24 and 40-43* is/are rejected.

7)☒ Claim(s) *38 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/30/2006 has been entered.

Claim Objections

Claims 38 and 42 are objected to because of the following informalities: "combinant" in line 3 should be "recombinant". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 24, and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

Amended claim 1 (from which claims 2-4 depend) recites a cassette expressed in the liver of a "post-natal subject". Applicant's response does not indicate where in the specification support for the amendment may be found. A review of the specification finds no mention of a cassette expressed in the liver of post-natal subjects. Therefore, there appears to be no support for the limitation "post-natal subject", nor evidence that applicants considered this limitation a part of their invention. Thus, the amended claims include impermissible New Matter.

Amended claim 24 (from which claims 40-43 depend) recites a cassette comprising an enhancer consisting of SEQ ID NO: 8. Applicant's response does not indicate where in the specification support for the amendment may be found. A review of the specification finds no mention of a cassette comprising only one, two, or three copies of SEQ ID NO: 8, which the instant claims encompass. All that is disclosed are vectors comprising four copies of SEQ ID NO: 8 (see [0014] of the published application, US 20020076798 A1). Therefore, there appears to be no support for cassettes comprising a hepatic locus control element comprising an enhancer consisting of SEQ ID NO: 8, wherein SEQ ID NO: 8 is present in more or less than four copies. Thus, the amended claims include impermissible New Matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: elements of the human FIX minigene found in the LX-ApoEenh-hAATp-FIXmg-bpA of Fig. 5 (i.e. the UTR of SEQ ID No: 7). A vector lacking

the additional elements of the hFIX minigene, LX-ApoEenh-hAATp-FIX-bpA (i.e. lacking the intron and UTR of SEQ ID NOs 1 and 7, respectively) did not express hFIX longer than 55 days. See Fig. 5.

Double Patenting

Applicant is advised that should claims 1 or 24 be found allowable, claims 16 and 43 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). **This rejection is maintained for reasons made of record and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 11/30/2006 have been fully considered but they are not persuasive. Applicants essentially assert that the claims are different in scope because claim 1, for example, recites that the cassette comprises a coding sequence comprising SEQ ID NO: 2 whereas claim 16, for example, recites that the coding sequence encodes a polypeptide consisting of SEQ ID NO: 3. Thus, the cassette of claim 1 could comprise additional coding sequences, such as reporter genes, that are not embraced by claim 16. Such is not the case. Even if the cassette of claim one where to recite a reporter gene, it would not be within the coding sequence recited in section (c) of the claim, but rather in a different coding sequence located elsewhere on the vector, and not likely within the same cassette. This is because of the intended use of the cassette for expressing hFIX in the mammalian liver, a use that does not include expressing

reporter genes. Furthermore, the claim recites, in section (c), "a Factor IX coding sequence", thus removing the possibility of the recited sequence from encoding any other sequence(s), such as reporter genes.

Claim 39 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 15. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 15 recites an expression cassette comprising the human Factor IX cDNA sequence, SEQ ID NO: 2. Thus, the cassette already encodes the Factor IX polypeptide set forth in SEQ ID NO: 3 and recited in claim 39. Also see the Double Patenting warning regarding claims 1, 24, 16, and 43 above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al (U.S. Patent 6,936,243) as evidenced by Simonet et al (1993 and 1994) and Nguyen et al (Oncogene, 1996) in view of Jallat et al (EMBO Journal, 1990) and Kurachi et al (J. Biol. Chem., 1995). **This rejection is maintained for reasons made of record in the Office Actions dated 12/12/2005, 5/30/2006, and for reasons outlined below.**

Response to Arguments

Applicant's arguments filed 11/30/2006 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the declaration of Inventor Mark Kay removes Synder et al as a 35 USC 102(e) reference; 2) the Kay declaration also presents evidence of unexpected results and an absence of a reasonable chance of success when combining the Snyder et al and Kurachi et al references.

Regarding 1), the declaration states that Dr. Kay was the sole inventor of the instantly claimed subject matter disclosed in the Snyder et al reference. Given this, the instant inventorship is still "by another" even if the inventorship of Snyder et al all is considered to be only Dr. Kay, due to Carol Miao also being listed as an inventor of the instant invention. Thus, Snyder et al is still an invention by another, and is considered prior art under 356 USC 102(e).

Regarding 2), the Kay declaration states that there is no reasonable expectation of success when using an intron to enhance the expression of a transgenic construct in post-natal animals,

and cites Brinster and Palmiter in support of this. However, both references detail the importance and desirability of using introns in transgenic constructs, contrary to the assertions of Dr. Kay, and neither reference discusses post-natal animals. All that is presented is a theory that expression *in vivo* may require the introns at some stage of development, a requirement not found in established cell lines. There are no teachings that the use of an intron in a transgenic construct in order to increase expression would be unpredictable, or have an unreasonable chance of success. To the contrary, many introns were found to enhance expression *in vivo*, see the abstracts of both references.

The Kay declaration discusses the results of Kurachi et al as only establishing the use of the endogenous Factor IX promoter together with the intron increased expression in tissue culture cells. Giver this, and according to publications of Dr. Kay, the regulation of expression cassettes in cultured cells versus *in vivo* in a liver is different. This is asserted as evidence that one of skill in the art would not know how to predict the behavior of promoters *in vivo* versus *in vitro*, and whether the use of the intron of Kurachi et al would enhance expression. Such assertions are not found convincing, primarily because they ignore the results of Jallat et al, who do establish the utility of the intron in question *in vivo* (see the previous Office Actions). The teachings of Jallet et al, taken with the results of Kurachi et al, remove nearly all doubt that addition of the intron to the constructs taught by Snyder et al would enhance expression of Factor IX. This is the opposite of applicant's assertions that there is no reasonable chance of success, rather, it would be surprising if the addition of the intron did not enhance expression of Factor IX, in direct contrast to the results of both Kurachi et al and Jallat et al (and, seemingly, Brinster

et al and Palmiter et al). Regarding the promoter used by Kurachi et al, this reference is not relied upon to teach the promoter of the invention, which is taught by Snyder et al.

The Kay declaration points to a paper detailing the instant invention, Miao et al, and states that, unexpectedly, inclusion of an intron in the expression constructs lead to no enhancement of Factor IX expression in tissue culture, but did enhance expression of Factor IX in post-natal animals. Again, given the results from four papers above, Brinster et al, Palmiter et al, Jallat et al, and Kurachi et al, it appears the use of introns in transgenic constructs in order to increase expression of the transgene was routine and predictable. It is therefore unclear what applicant believes is unexpected about such an increase in expression when an intron is used in the instant invention. A reading of Miao et al indicates the authors (including Dr. Kay) believed the inclusion of an intron would enhance expression of the Factor IX transgene, see ¶ linking pages 522-523, and the following ¶.

Finally, the Kay declaration submits that there is no significant influence on expression in vivo when the cassette is constructed without the UTR. It is unclear how this statement is relevant to the instant rejection, as this UTR element is not recited in the instant claims. Furthermore, the Miao et al reference would seem to refute this statement, as the authors believed the UTR to enhance Factor IX expression two-fold versus use of the bovine polyA sequence. See Miao et al, page 531, first column, first full ¶.

Conclusion

Claims 15, 36, and 37 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER